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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/527,785	10/03/2005	Marco Cattaruzza	DEBE:053US/10501498	1068

32425 7590 01/22/2009

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EXAMINER	
WOLLENBERGER, LOUIS V	

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
01/22/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/527,785	CATTARUZZA ET AL.	
	Examiner	Art Unit	
	Louis Wollenberger	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 December 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/18/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 12/1/2008 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 6/9/2008 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-3 are pending and under examination.

Information Disclosure Statement

Applicant's IDS of 6/18/08 is acknowledged. The reference cited therein as Asif et al. (C15) could not be considered because no date has been provided for the reference. See 37 CFR 1.98(b)(5).

Claim Objections

Claim 1 is objected to because of the recitation "up to approximately 30 bases," a limitation added by amendment on 11/29/2007. Strictly speaking the amendment is not adequately supported the specification as filed, which is drawn to "double stranded" decoy oligonucleotides. See page 6. Accordingly, the specification supports limitations to length in units of "base pairs," not ---bases--- as now written. See page 17. Given that SEQ ID NO:17 and 18 are each 16 bases in length, and given the lack of any language in the claim defining the decoy as double stranded, the language "up to approximately 30 bases" is somewhat confusing in view of possible end-to-end structures comprising at least 32 bases in length, which the claim

reasonably embraces as now written. It is respectfully suggested written description support exists at page 17 of the specification for the limitation "up to a length of approximately 30 base pairs." Correction is requested.

Non-Statutory Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1 and 2 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 11-19 of copending Application No. 10/526430. Although the conflicting claims are not identical, they are not patentably distinct from each other because conflicting application 10/526430 claims a pharmaceutical formulation comprising a nucleic acid and a nonsteroidal anti-inflammatory drug.

MPEP §804 provides that "…those portions of the specification which provide support for the patent claims may also be examined and considered when addressing the issue of whether

a claim in the application defines an obvious variation of an invention claimed in the patent. *In re Vogel*, 422 F.2d 438, 441-42, 164 USPQ 619, 622 (CCPA 1970). The court in *Vogel* recognized "that it is most difficult, if not meaningless, to try to say what is or is not an obvious variation of a claim," but that one can judge whether or not the invention claimed in an application is an obvious variation of an embodiment disclosed in the patent which provides support for the patent claim.

35 USC 112, first paragraph, support for claims 11-19 of copending application 10/526430 finds that the "nucleic acid" may be a decoy olignucleotide of the type comprising or identical to that now claimed. An updated STIC-Biotech sequence search of instant SEQ ID NO:17 finds that the double stranded oligonucleotides corresponding to SEQ ID Nos. 1, 2, 5, 6, 13, 14, 17, 18, and 37 each comprise instant SEQ ID NO:17. See selected alignments below.

Thus, given that the "nucleic acid" recited in claims 11-19 of 10/526430 may be any one of the decoy oligonucleotides disclosed in the 10/526430 specification, and given that the instantly claimed decoy is intended for pharmaceutical use to treat an inflammatory condition, such as arthritis, one of ordinary skill in the art would conclude that the invention defined in claims 1 and 2 is anticipated by, or would have been an obvious variation of, the invention defined in a claim in the conflicting application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

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RESULT 3
US-10-526-430A-17
; Sequence 17, Application US/10526430A
; Publication No. US20060258601A1
; GENERAL INFORMATION:
;  APPLICANT: BECKER, MARKUS
;  APPLICANT:  WAGNER, ADREAS H.
;  TITLE OF INVENTION: Functional correction of the -786C/T-variance of the human eNOS-gene
;  FILE REFERENCE: DEBK:052US
;  CURRENT APPLICATION NUMBER: US/10/526,430A
;  CURRENT FILING DATE:  2005-03-01
;  PRIOR APPLICATION NUMBER: PCT/DE 03/02901
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;  PRIOR FILING DATE: 2003-09-12
;  PRIOR APPLICATION NUMBER: DE 102 42 319
;  PRIOR FILING DATE: 2002-09-12
;  NUMBER OF SEQ ID NOS: 63
;  SOFTWARE: PatentIn version 3.1
; SEQ ID NO 17
;   LENGTH: 16
;   TYPE: DNA
;   ORGANISM: Artificial Sequence
;   FEATURE:
;   OTHER INFORMATION: Decoy-Oligonucleotide
US-10-526-430A-17

  Query Match           100.0%;  Score 16;  DB 14;  Length 16;
  Best Local Similarity  100.0%;  Pred. No. 9e+02;
  Matches   16;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 TCCCTGGCCGGCTGAC 16
              ||||||||||||||||
Db          1 TCCCTGGCCGGCTGAC 16


RESULT 4
US-10-526-430A-18/c
; Sequence 18, Application US/10526430A
; Publication No. US20060258601A1
; GENERAL INFORMATION:
;  APPLICANT: HECKER, MARKUS
;  APPLICANT:  WAGNER, ANDREAS H.
;  TITLE OF INVENTION: Functional correction of the -786C/T-variance of the human eNOS-gene
;  FILE REFERENCE: DEBE:052US
;  CURRENT APPLICATION NUMBER: US/10/526,430A
;  CURRENT FILING DATE:  2005-03-01
;  PRIOR APPLICATION NUMBER: PCT/DE 03/02901
;  PRIOR FILING DATE: 2003-09-12
;  PRIOR APPLICATION NUMBER: DE 102 42 319
;  PRIOR FILING DATE: 2002-09-12
;  NUMBER OF SEQ ID NOS: 63
;  SOFTWARE: PatentIn version 3.1
; SEQ ID NO 18
;   LENGTH: 16
;   TYPE: DNA
;   ORGANISM: Artificial Sequence
;   FEATURE:
;   OTHER INFORMATION: Decoy-Oligonucleotide
US-10-526-430A-18

  Query Match           100.0%;  Score 16;  DB 14;  Length 16;
  Best Local Similarity  100.0%;  Pred. No. 9e+02;
  Matches   16;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 TCCCTGGCCGGCTGAC 16
              ||||||||||||||||
Db         16 TCCCTGGCCGGCTGAC 1


RESULT 8
US-10-526-430A-13
; Sequence 13, Application US/10526430A
; Publication No. US20060258601A1
; GENERAL INFORMATION:
;  APPLICANT: HECKER, MARKUS
;  APPLICANT:  WAGNER, ANDREAS H.
;  TITLE OF INVENTION: Functional correction of the -786C/T-variance of the human eNOS-gene
;  FILE REFERENCE: DEBE:052US
;  CURRENT APPLICATION NUMBER: US/10/526,430A
;  CURRENT FILING DATE:  2005-03-01
;  PRIOR APPLICATION NUMBER: PCT/DE 03/02901
;  PRIOR FILING DATE: 2003-09-12
;  PRIOR APPLICATION NUMBER: DE 102 42 319
;  PRIOR FILING DATE: 2002-09-12
;  NUMBER OF SEQ ID NOS: 63
;  SOFTWARE: PatentIn version 3.1
; SEQ ID NO 13
;   LENGTH: 19
;   TYPE: DNA
;   ORGANISM: Artificial Sequence
;   FEATURE:
;   OTHER INFORMATION: Decoy-Oligonucleotide
US-10-526-430A-13

  Query Match           100.0%;  Score 16;  DB 14;  Length 19;
  Best Local Similarity  100.0%;  Pred. No. 8.6e+02;
```

```
  Matches   16;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 TCCCTGGCCGGCTGAC 16
              ||||||||||||||||
Db          4 TCCCTGGCCGGCTGAC 19


RESULT 9
US-10-526-430A-14/c
; Sequence 14, Application US/10526430A
; Publication No. US20060258601A1
; GENERAL INFORMATION:
;  APPLICANT: HECKER, MARKUS
;  APPLICANT:  WAGNER, ANDREAS H.
;  TITLE OF INVENTION: Functional correction of the -786C/T-variance of the human eNOS-gene
;  FILE REFERENCE: DEBE:052US
;  CURRENT APPLICATION NUMBER: US/10/526,430A
;  CURRENT FILING DATE:  2005-03-01
;  PRIOR APPLICATION NUMBER: PCT/DE 03/02901
;  PRIOR FILING DATE: 2003-09-12
;  PRIOR APPLICATION NUMBER: DE 102 42 319
;  PRIOR FILING DATE: 2002-09-12
;  NUMBER OF SEQ ID NOS: 63
;  SOFTWARE: PatentIn version 3.1
; SEQ ID NO 14
;   LENGTH: 19
;   TYPE: DNA
;   ORGANISM: Artificial Sequence
;   FEATURE:
;   OTHER INFORMATION: Decoy-Oligonucleotide
US-10-526-430A-14

  Query Match             100.0%;  Score 16;  DB 14;  Length 19;
  Best Local Similarity   100.0%;  Pred. No. 8.6e+02;
  Matches   16;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 TCCCTGGCCGGCTGAC 16
              ||||||||||||||||
Db         16 TCCCTGGCCGGCTGAC 1


RESULT 10
US-10-526-430A-37/c
; Sequence 37, Application US/10526430A
; Publication No. US20060258601A1
; GENERAL INFORMATION:
;  APPLICANT: HECKER, MARKUS
;  APPLICANT:  WAGNER, ANDREAS H.
;  TITLE OF INVENTION: Functional correction of the -786C/T-variance of the human eNOS-gene
;  FILE REFERENCE: DEBE:052US
;  CURRENT APPLICATION NUMBER: US/10/526,430A
;  CURRENT FILING DATE:  2005-03-01
;  PRIOR APPLICATION NUMBER: PCT/DE 03/02901
;  PRIOR FILING DATE: 2003-09-12
;  PRIOR APPLICATION NUMBER: DE 102 42 319
;  PRIOR FILING DATE: 2002-09-12
;  NUMBER OF SEQ ID NOS: 63
;  SOFTWARE: PatentIn version 3.1
; SEQ ID NO 37
;   LENGTH: 19
;   TYPE: DNA
;   ORGANISM: Artificial Sequence
;   FEATURE:
;   OTHER INFORMATION: DNA Oligonucleotide
US-10-526-430A-37

  Query Match             100.0%;  Score 16;  DB 14;  Length 19;
  Best Local Similarity   100.0%;  Pred. No. 8.6e+02;
  Matches   16;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 TCCCTGGCCGGCTGAC 16
              ||||||||||||||||
Db         18 TCCCTGGCCGGCTGAC 3
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Response to Arguments

Applicant submits if the instant ODP rejection should be withdrawn in the first application, allowing the first application to be passed to issue, but does not state which application Applicant considers to be "the first application." MPEP 804 states "If a "provisional" nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer."

Based on the STIC-Biotech Sequence searches to date, it would appear that the decoy comprising SEQ ID NO:17 and 18 was not disclosed in either PCT/DE03/02901 (WO/2004/022102) or German Application 10240418.6 to which US Application 10/526430 claims priority. On the other hand the STIC search does find SEQ ID NO:17 in PCT/DE03/03028 (WO/2004/027062) and German Application 10242319.9 to which the instant application, 10/527785 claims priority. Therefore, it would appear that the instant application is the "earlier-filed application" for purposes of the claimed invention. However, the instant ODP rejection is not the only rejection remaining in the instant application and is therefore maintained.

Claim Rejections - 35 USC § 112, first paragraph (Enablement)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 3 remains rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in a determination of lack of enablement include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

The claim is drawn to a method of treating coronary heart disease and rheumatoid arthritis by delivery of a decoy oligonucleotide comprising SEQ ID NO:17 and 18.

Therefore the invention requires delivery and uptake of a nucleic acid into cells and tissues in vivo in an amount necessary to produce a therapeutic effect, wherein said effect is directly relevant to symptoms and conditions associated with coronary heart disease and rheumatoid arthritis.

A careful review of the specification finds no in vivo working examples representative of the claimed method. No instances in the prior art are found describing the use of the claimed decoy to treat any disease. No nexus has been established between the biological effects mediated by the decoy in vitro and the therapeutic effect claimed in vivo.

The specification at page 38, Table 3, shows that a decoy oligonucleotide comprising SEQ ID NO:17 is capable of restoring the inhibitory effect of IL-10 on the CD154-induced IL-12 p40 mRNA expression in endothelial cells from donors with the -786 C/C genotype in the eNOS gene. The SNP is said to affect the amount of nitric oxide production of endothelial cells. IL-10 is said to play a role in eNOS expression. Applicant then concludes on the basis of these data and a proposed link between the -786C/C genotype and RA and CHD (Tables 1 and 2, pages 31-32), restoration of the anti-inflammatory activity of IL-10 in cells in vivo by administration of said decoy would be remedial to conditions associated with a host of inflammatory diseases, including rheumatoid arthritis and coronary heart disease.

However, there is no evidence suggesting that the biochemical effects observed in vitro in cultured cells would translate to a therapeutic effect in vivo in a subject in need. Applicant does not provide any evidence that the restorative effects observed in vitro with regard to p40 mRNA expression would correlate with any type of treatment effect in vivo. A sufficient link between the biochemical pathway said to be altered by the decoy in cells in vitro and the effects representative of therapy in a person is absent. Instead, Applicant relies on complex array of facts and evidence available in the prior art and disclosed in the specification loosely correlating the activities of interleukins, various transcription factors, eNOS expression and the symptoms associated with arthritis and coronary heart disease.

The problem is that no direct nexus has been established between the biological effects observed in cells in vitro and the therapeutic effects claimed. How or if the in vitro effects would be manifested in a patient are completely unknown. Given the lack of complete understanding as to the many different factors that may potentially cause or contribute to RA and CHD in any patient, the presumption that the restoration of IL-10 activity in cells in vitro may be used to alleviate one or more symptoms associated with RA or CHP is speculative.

Additionally, the prior art is replete with evidence suggesting the delivery of nucleic acids to cells in vivo was challenging. Applicant provides no direction or guidance as to how or even whether the claimed decoys may be delivered into cells in vivo, particularly cells in the synovial lining, in an amount and for a sufficient time to produce a therapeutic effect. Depending on the mode, delivery itself may exacerbate the very symptoms the decoy is designed to alleviate. The disclosure provides no direction as to how to deliver the decoy so as to achieve the claimed effect. As a result, one of skill would have no assurance the claimed effects could be obtained without engaging in undue experimentation.

Furthermore, while the prior art suggests that nucleic acids may be delivered into the synovial lining by direct injection, the specification provides no evidence, guidance, or direction as to how to deliver the decoy into synovial fluids or cells via systemic administration, which is a mode currently embraced by the claim. Moreover, the prior art suggests that non-viral delivery to cells in the synovium is low and viral-mediated delivery while feasible suffers from unreliable or short-lived expression of the transgene. See Ghivizzani et al. (2001) *DDT* 6:259-267, who state that RA has proven to be an exceedingly difficult disease to treat. "In general, high doses of drugs are necessary to achieve therapeutic levels in the joint, and many agents that are effective

in providing symptomatic relief require repeated administration, often with unpleasant side effects." (page 259).

While the instant application reasonably identifies a potential molecular biological link between eNOS expression, the -786C/C genotype, and certain inflammatory diseases such as RA and CHD, the biochemical link and in vitro data represent nothing more than a starting point for further research, which would be necessary to establish whether the conditions of RA and CHD in a patient (e.g., animal model) would be effectively treated by administration of the instant decoy in the manner proposed by applicant.

Therefore, considering the breadth of the claims, the state of the art at the time of filing, the level of unpredictability in the art, and the limited guidance and working examples provided by the instant application, the Examiner submits that the skilled artisan would be required to conduct undue, trial and error experimentation to practice the claimed invention commensurate with the claims scope.

Accordingly, the instant claims are rejected for failing to comply with the enablement requirement.

Response to Arguments

Applicant's arguments filed 12/1/2008 have been fully considered but are not persuasive.

To summarize, it remains the Examiner's position that while Applicant may have reasonably identified a genetic marker, or polymorphism, in the eNos gene associated with individuals predisposed to or currently suffering from coronary heart disease and possibly rheumatoid arthritis, Applicant has not taught or reasonably established any nexus between the

addition or administration of the claimed oligonucleotide decoys comprising the polymorphic site and the alleviation or treatment of coronary heart disease and rheumatoid arthritis in said individuals. The specification speculates an inhibitory transcription factor binds at the polymorphic site and inhibits proper eNos expression, but never fully identifies the factor or shows that such a factor exists. The specification shows at Figs. 3 that C-type decoys but not T-type decoys restore shear stress induction of eNOS in cultivated endothelial cells with the homozygous C/C -786 genotype. However, this demonstration is not representative of the treatment of either coronary heart disease or arthritis or of the population of individuals embraced by the claim, which may have the disease but not the SNP, or that may be only heterozygous for the polymorphism.

The specification shows at Fig. 6 and page 38 that decoys can restore IL-10 mediated inhibition of IL-12 synthesis, a potential anti-inflammatory effect. See pages 12 and 13. However, this example is not representative of treatment of either coronary heart disease or arthritis in vivo. Thus, while Applicant may have established a nexus between administration of the instantly claimed decoys and enhanced eNOS expression in endothelial cells and restoration of IL-10 mediated inhibition of IL-12 synthesis in vivo, Applicant has not provided the direction and guidance needed to enable one of skill to use the decoy oligonucleotide in the manner claimed to treat individuals with coronary heart disease and arthritis. The data disclosed in the specification provide a starting point for further research, wherein the effects on eNOS expression and IL-10 activity observed in endothelial cells in culture after exposure to the decoy suggest that the same effects may be obtained in endothelial cells in vivo. However, the fact that endothelial cells are involved in many different inflammatory diseases, such as CHD and RA,

and the finding of a genetic correlation between the SNP and such diseases, does not provide the necessary guidance to enable one of skill to treat CHD and RA with the decoys with any reasonable assurance of obtaining a positive therapeutic effect. It is implied that increased expression of eNOS through the use of the decoy and restoration of IL-10 activity is evidence coupled with the fact the decoy sequence comprises the SNP correlated with the target disease is evidence that CHD and RA can be treated. However, the evidence is indirect, and the function asserted by the claim, speculative.

While in vivo models are not necessary to enable the invention, it is reasonable to question the enablement of a method in viov based on in vitro models that are so far removed from the in vivo environment and conditions and based on limited biochemical data which may or may not suggest a possible therapeutic strategy. Nevertheless, Applicant has reasonably established a nexus between decoy administration and the increase in eNOS expression in certain cell types using certain decoy types. An increase in eNOS expression is not necessarily correlative of treatment of heart disease or arthritis, and Applicant provides no evidence reasonably to suggest otherwise.

Applicant's remarks regarding the lack of adequate animal models in which to test or confirm the use of the decoy in the manner now claimed are well taken. However, the fact that such models are lacking does not remove the need for enabling disclosure. Granting Applicant the right to exclude others from making and using the decoys in the manner now claims would preempt the future without the quid pro quo required by law.

Clearly, IL-10, IL-12, eNOS and a host of other factors contribute to a plethora of inflammatory diseases, including those specifically recited in the claims. However, the Examiner

finds no evidence teaching or suggesting that genetic markers or risk factors are also most likely drug targets which may be used to treat the disease. They represent starting points for further research. Applicant points to IL-10 supplementation, or gene therapy, in IL-10 deficient mice as a treatment of atherosclerosis. However, the instant decoys have not been shown to increase IL-10 expression in any cell or reduce atherosclerotic plaque formation or size.

Thus, while the instant specification in conjunction with the prior art reasonably enables methods of using the instant decoy in vivo to achieve certain well defined effects described in the application, the effects are specific in nature, having to do, perhaps, with changes in eNOS expression under certain conditions and changes in IL-10/IL-12 activity in certain individuals having a specific genotype. Evidence clearly linking the described effects in vitro with a more general result in vivo that is directly attributable to these effects may be remedial with regard to a more general method such as increasing eNOS expression or inhibiting IL-12 synthesis in a subject having the described genotype, noting that the genotype must be specifically defined in the specification and shown to be targeted by the instant decoy.

Finally, and importantly, the specification and Applicant's remarks are entirely directed to a proposed therapy in individuals hetero- and homo-zygous for the -786 C/T mutation. However, claim 3 as now written reads on <u>any</u> subject in need thereof, including subjects suffering from CHD or RA but for reasons wholly unrelated to the -786 C/T mutation. For example, the claim reads on subjects having no detectable mutation (SNP) but nevertheless suffering from CHD and RA. The instant application provides no evidence reasonably commensurate with the assertion that the instant decoys may be used to treat these individuals, i.e., individuals who do not display the C/T genotype.

Accordingly, while Applicant's remarks traversing the enablement rejection have been fully considered, they are not persuasive in view of the breadth of the claim and the lack of guidance and direction in the disclosure reasonably enabling one of skill to practice the method commensurate in scope with what is now claimed.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis Wollenberger whose telephone number is (571)272-8144. The examiner can normally be reached on M-F, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571)272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Louis Wollenberger/
Examiner, Art Unit 1635
January 17, 2009